IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	CHERN et al.
Serial No.	:	09/271,098
Filing Date	:	March 18, 1999
For	:	*IMPROVED LIQUID POLYMERIC COMPOSITIONS FOR CONTROLLED RELEASE OF BIOACTIVE SUBSTANCES*
Examiner	:	Shahnam J. Sharaeh
Art Unit	:	1617

#34 HKD 5-14-03

DECLARATION OF DR. MARK SOLL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Dr. MARK SOLL DECLARES AND SAYS THAT:

I am qualified to speak as to the instant invention and the data presented

1. My *Curriculum vitae* is attached as Exhibit A. I respectfully submit that I am skilled in the art to which the present application pertains. I am advised that claims previously pending in this application were rejected as obvious. I further understand that claims now pending are directed to polymeric (poly(lactide-co-glycolide) copolymer or "PLGA polymer") controlled release compositions ("LAI compositions") containing eprinomectin as the active substance, as set forth, or as substantially set forth, in Exhibit B. In addition, work reported herein was performed under my direction, supervision or control in the ordinary course of business. I respectfully submit that I am thus qualified to introduce the work reported herein. I further respectfully submit that in view of my education, training and experience, as well as my understanding as to the now pending claims, and my ability to speak as to the work reported herein, that I am qualified to render opinions as to the state of the art to which the present invention pertains and as to the present invention.

2. More specifically, this Declaration is submitted in support of the patentability of the now pending claims; and, I respectfully submit that the now pending claims are patentable as the presently claimed invention is nonobvious and surprising because one skilled in the art cannot predict whether a particular active substance will function in a LAI composition, for instance, as shown by the data below, wherein the eprinomectin LAI compositions of the present

invention function for their intended purpose whereas emamectin LAI compositions do not (showing that one cannot assert that it would have been obvious to use one or another active substance in an LAI composition and that a particular active substance indeed is functional in an LAI composition is surprising and unexpected, rendering the instant claims patentable).

The superior utility of the instant invention

3. Eprinomectin (4"-epi-acetylamino-4"-deoxy-avermectin B_1), a member of the avermectin family, is a potent endectocide that is the active ingredient in IVOMEC EPRINEX Pour-On for cattle. In the pour-on formulation at a dose of 500 mcg/kg, it has been shown to have excellent efficacy against a wide variety of internal and external parasites. Eprinomectin LAI compositions of the present invention form a subcutaneous matrix that slowly breaks down, releasing the drug into the circulation. Studies in cattle challenged with various internal parasites have shown that compositions of the instant invention can achieve plasma levels for over 120 days which result in >90% efficacy. The ability of formulations of the instant invention to achieve a continued, potent, eprinomectin plasma level for up to 4 months makes the inventive formulations attractive for the treatment of internal parasites for animals on pasture. One injection can provide season-long treatment of internal parasites.

Studies of eprinomectin LAI compositions and emamectin LAI compositions

4. Studies of formulations of eprinomectin and PLGA polymer and emamectin and PLGA polymer were performed in cattle.

a. The eprinomectin and PLGA polymer compositions contain 5% eprinomectin, 5% 75:25 PLGA, differing only in their liquid vehicles, with one containing N-methylpyrrolidone and triacetin and one containing only triacetin as the liquid vehicle.

Eprinomectin LAI formulation 1

5.0% w/v	Eprinomectin
5.0% w/v	PLGA75:25
0.02% w/v	BHT
30% v/v	N-Methyl Pyrrolidone (NMP)
QS 100% v/v	Triacetin

Eprinomectin LAI formulation 2

5.0% w/v	Eprinomectin
5.0% w/v	PLGA75:25
0.02% w/v	BHT
QS 100% v/v	Triacetin

Emamectin and PLGA compositions were similarly formulated.

b. The formulations are each a clear viscous liquid, in which all solid ingredients are molecularly dissolved in a liquid vehicle. One of the solid excipients is a biodegradable polymer, poly(lactide-co-glycolide). Upon subcutaneous injection into the cattle and exposure to body fluid, a portion of the polymer precipitates and forms a continuous thin film encapsulating the formulation. The encapsulated formulation gradually turns into a semi-solid depot as the liquid vehicle diffuses away from the injection site, leaving behind the remaining less soluble ingredients, including the drug that is entrapped in the polymer. During this initial period, some drug is delivered from the depot by way of diffusion. Over time, the hydrolysis-prone polymer gradually breaks down into smaller and smaller segments and becomes more soluble in the body fluid, thus introducing erosion as an additional route of drug delivery.

c. In all studies, a similar experimental design was used. Young cattle ranging in weight from about 100-300 kg were given a single subcutaneous administration of the formulation, at a dose of 1 mg/kg of eprinomectin or emamectin. Generally the dose volume was less than 5 ml. Plasma levels were monitored by taking weekly blood samples.

d. Emamectin was not a satisfactory active in a LAI formulation. It caused injection site reactions in all cattle, and plasma levels were significantly below those achieved with eprinomectin in the similar eprinomectin LAI formulation. The release profile of the emamectin was significantly different from eprinomectin–lower plasma levels were achieved, and the duration of release was considerably less. Accordingly, emamectin was not suitable for an active substanced in a LAI formulation.[1]

e. In contrast, good plasma levels were achieved in the groups of cattle treated with the eprinomectin LAI formulations. Efficacy was achieved with Day 120 plasma levels approximately >2 ng/ml.[2]

---

[1] In this regard, it is noted that I am advised that the instant application only mentions the use of emamectin as an active substance in a LAI composition with another active substance in the LAI composition, whereas eprinomectin and ivermectin are exemplified active substances in LAI compositions.

[2] All graphs are presented in two forms –(a) has a Y axis scale of 0-60 ng/ml and shows the overall plasma data, including Cmax: (b) has the same data, graphed on a Y axis scale of 0-20 ng/ml with days 14-147 shown. This makes it easier to examine the trough plasma levels throughout the study.

Figure 1a. Mean plasma levels from cattle treated with 5% eprinomectin LAI over 140 days. Groups 2 and 3: NMP/triacetin formulation, Groups 4 and 5: triacetin alone. Groups 2 and 4 injected in front of the shoulder, Groups 3 and 5 behind the shoulder.

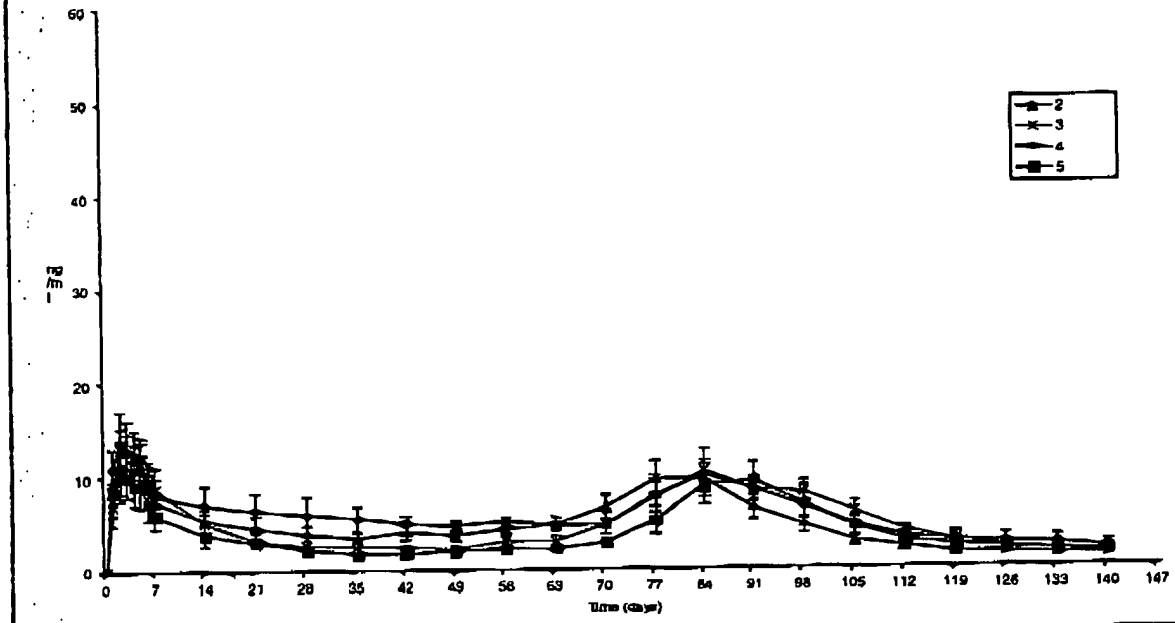
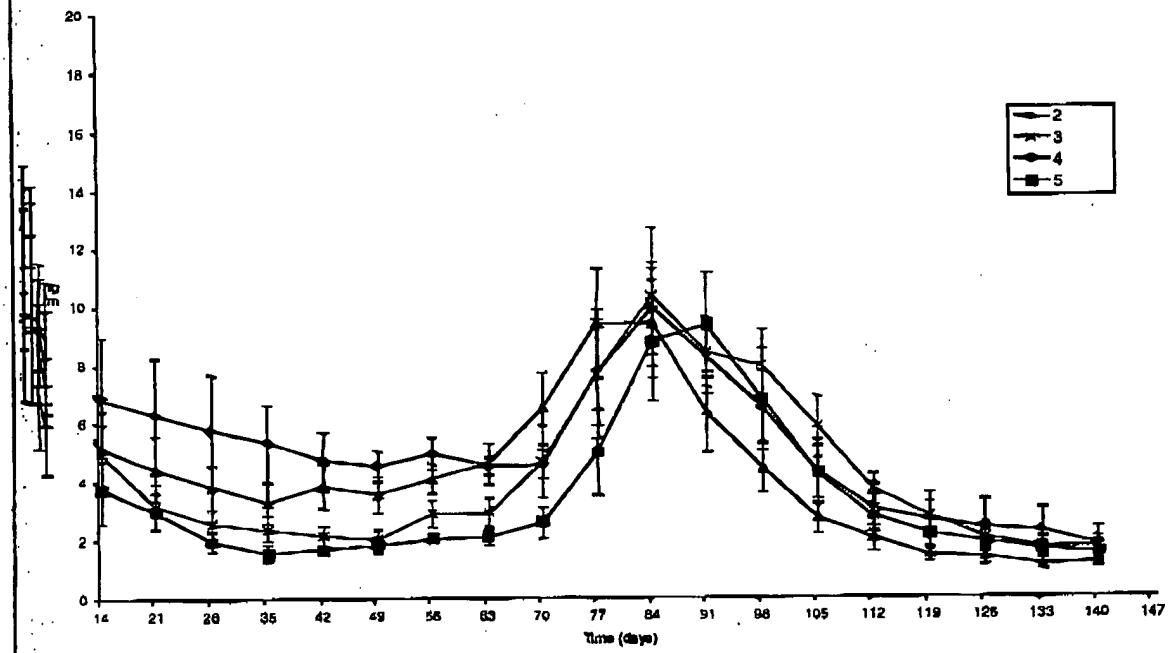


Figure 1b. Mean plasma levels from cattle treated with 5% eprinomectin LAI from Day 14 to Day 140. Groups 2 and 3: NMP/triacetin formulation, Groups 4 and 5: triacetin alone. Groups 2 and 4 injected in front of the shoulder, Groups 3 and 5 behind the shoulder.



f. Based on the above data formulation 1, which contains 5% eprinomectin, 5% 75:25 PLGA in NMP/triacetin was injected in groups of cattle behind the shoulder. Plasma levels were consistent with those seen in previous studies, showing an initial peak, followed by a secondary peak around Day 90. In Figures 2a and b below, plasma data from three studies are compared.

Figure 2a. Mean plasma levels from Group 11 (n=3), Group 3 (n=6) and Group 2 (n=6). All animals were treated with formulation 1 behind the shoulder. Groups 11 and 3 were necropsied on approximately Day 147, Group 2 on Day 91.

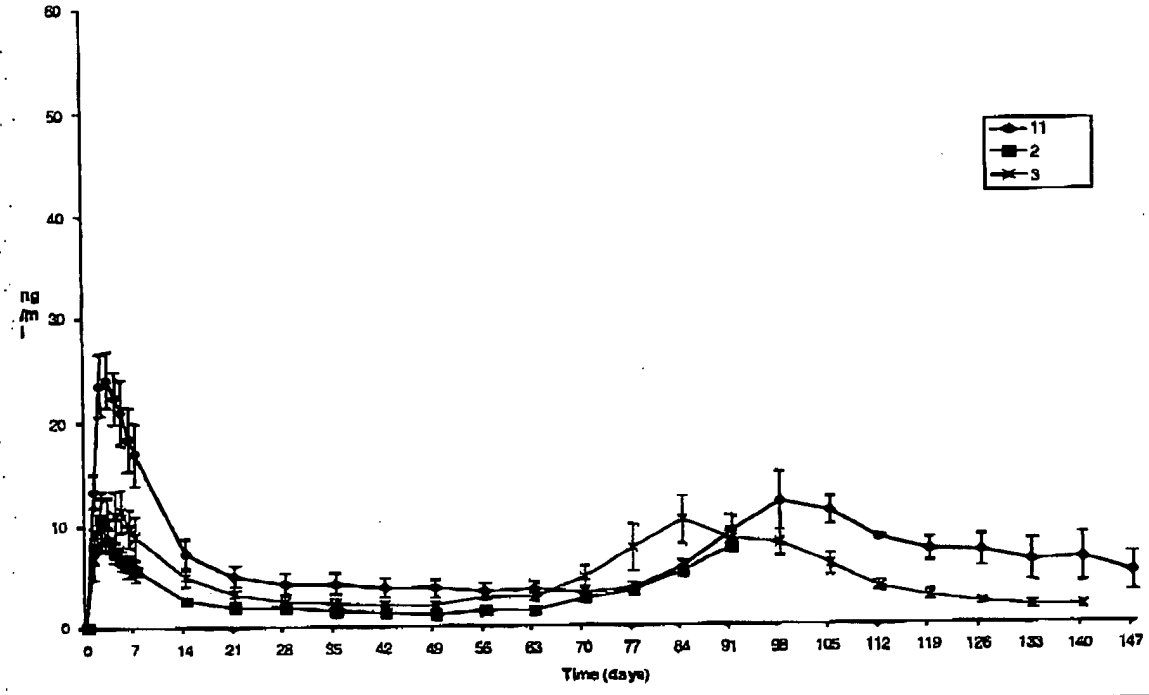
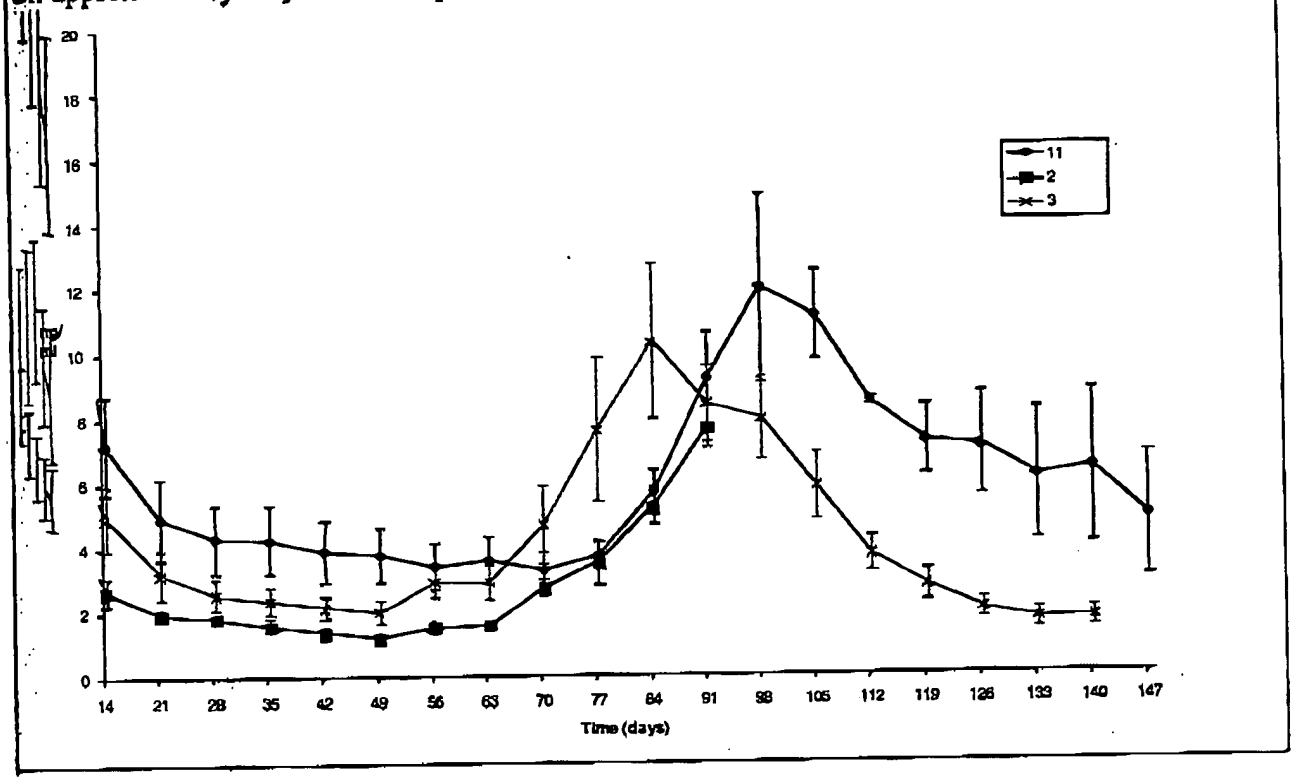


Figure 2b. Mean plasma levels from Group 11 (n=3), Group 3 (n=6) and Group 2 (n=6). All animals were treated with formulation 2 behind the shoulder. Groups 11 and 3 were necropsied on approximately Day 147, Group 2 on Day 91.



g. In eprinomectin LAI formulations, the polymer ratio of 75:25 gives high terminal plasma levels with a secondary peak occurring at around Day 90-100. While formulations containing 75:25 polymer are especially advantageous, formulations similar to formulations 1 and 2 herein but containing 65:35 polymer were also tested and are also useful because in those studies (similar to the studies reported herein), the formulations provided eprinomectin plasma levels, with the secondary peak occurred around Day 60. Furthermore, it is appreciated that claims being presented may call for formulations containing 1 to 10% eprinomectin and 1 to 10% PLGA. The results reported herein involve formulations containing 5% eprinomectin and 5% PLGA. Similar good results, e.g., eprinomectin plasma levels, were obtained in studies (similar to the studies reported herein) using formulations containing 10% eprinomectin and 10% PLGA, as well as in studies (similar to the studies reported herein) using formulations containing 2.5% eprinomectin and 2.5% PLGA. Thus, it is respectfully submitted that the ranges that may be recited in the claims presented encompass many embodiments that provide results as herein or analogous to results herein, e.g., eprinomectin plasma levels. And

again, it is noted that emamectin LAI formulations were not considered suitable as significantly low plasma levels were achieved by emamectin LAI formulations (making them unsuitable to proceed with challenge experiments, *see infra*). Accordingly, the presently claimed invention is nonobvious as it provides unexpected results; results that could not have been predicted.

h. Cattle given eprinomectin LAI formulations 1 and 2 of the invention were challenged, around Day 120, with *Cooperia, Ostertagia, Nematodirus* and *Haemonchus* larvae. Approximately one month after challenge (see graphs above), animals were necropsied for nematode recovery and tissues collected for residue analysis. All treated groups showed excellent efficacy (>90%). Group 3 had significantly ($p<0.05$) better efficacy (99% efficacy against *Haemonchus*) than Group 2 (90%), showing that although the higher mean plasma levels were not statistically significant, they were biologically significant. Accordingly, the inventive formulations are suitable for prevention of parasites; and, this is surprising and unexpected because one could not predict this result, especially considering the result achieved with emamectin. Therefore, the present invention is not obvious.

The present invention is therefore not obvious

5. It is therefore respectfully submitted that the inventive eprinomectin LAI compositions are not obvious as one could not have predicted that they would have achieved the results that they do, e.g., plasma levels, prevention of parasites, especially as one cannot predict whether any particular active substance will be effective in a LAI composition, e.g., as shown by the unsuitable results with the emamectin LAI compositions.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 5 MAY 2003

By: Mark D. Soll.
MARK D. SOLL, DVM, MMedVet, MRCVS